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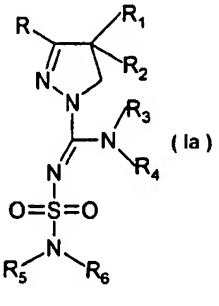
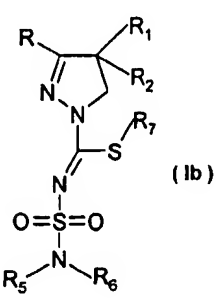
(54) Title: 4,5-DIHYDRO-1H-PYRAZOLE DERIVATIVES HAVING POTENT CB1-ANTAGONISTIC ACTIVITY



(Ia)



(Ib)

(57) Abstract: The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives which are potent cannabinoid (CB_1) receptor antagonists with utility for the treatment of diseases connected with disorders of the cannabinoid system. The compounds have the general formula (Ia) or (Ib) wherein the symbols have the meanings given in the specification. The invention also relates to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

4,5-Dihydro-1H-pyrazole derivatives having potent CB_1-antagonistic activity

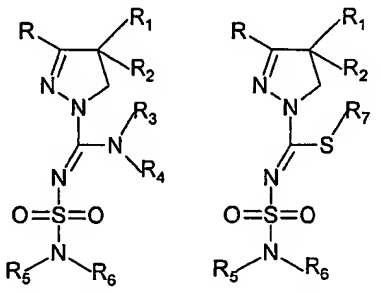
The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

The above mentioned 4,5-dihydro-1H-pyrazoles are potent cannabinoid (CB_1) receptor antagonists with utility for the treatment of disorders involving cannabinoid neurotransmission.

Cannabinoids are present in the Indian hemp *Cannabis sativa* and have been used as medicinal agents for centuries (Mechoulam, R. and Feigenbaum, J.J. *Prog. Med. Chem.* **1987**, *24*, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of cannabinoid receptors (CB_1 and CB_2) stimulated the search for novel cannabinoid receptor antagonists (Munro, S. *et al.*, *Nature* **1993**, *365*, 61. Matsuda, L.A. and Bonner, T.I. *Cannabinoid Receptors,* Pertwee, R.G. Ed. **1995**, 117, Academic Press, London). In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system (Consroe, P. *Neurobiology of Disease* **1998**, *5*, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* **1999**, *1*, 587. Greenberg, D.A. *Drug News Perspect.* **1999**, *12*, 458. Pertwee, R.G., *Progress in Neurobiology* **2001**, *63,* 569). Hitherto, several CB_1 receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB_1 receptor antagonists. A representative example is SR-141716A (Dutta, A.K. *et al., Med. Chem. Res.* **1994**, *5*, 54. Lan, R. *et al., J. Med. Chem.* **1999**, *42*, 769. Nakamura-Palacios, E.M. *et al., CNS Drug Rev.* **1999**, *5*, 43). CP-272871 is a pyrazole derivative, like SR141716A, but less potent and less CB_1 receptor subtype-selective than SR141716A (Meschler, J.P. *et al., Biochem. Pharmacol.* **2000**, *60,* 1315). Aminoalkylindoles have been disclosed as CB_1 receptor antagonists. A representative example is Iodopravadoline (AM-630), which was introduced in 1995. AM-630 is a moderately active CB_1 receptor antagonist, but sometimes behaves as a weak partial agonist (Hosohata, K. *et al., Life Sc.* **1997**, *61*, PL115). Researchers from Eli Lilly described aryl-aroyl substituted benzofurans as selective CB_1 receptor antagonists (*e.g.* LY-320135) (Felder, C.C. *et al., J. Pharmacol. Exp. Ther.* **1998**, *284,* 291). 3-Alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M. *et al., Biorg. Med.Chem. Lett.* **1999**, *9,* 2233). Aventis Pharma claimed diarylmethyleneazetidine analogs as CB_1 receptor antagonists (Mignani, S. *et al.,* Patent FR 2783246, 2000; *Chem. Abstr.* **2000**, *132,* 236982). Tricyclic pyrazoles were claimed by Sanofi-Synthelabo as CB_1 antagonists (Barth, F. *et al.,* Patent WO 0132663, 2001; *Chem. Abstr.* **2001**, *134,* 340504). Interestingly, many CB_1 receptor

antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R.S. *et al., Eur. J. Pharmacol.* **1997**, *334*, R1). Reviews provide a nice overview of the cannabinoid research area (Mechoulam, R. *et al., Prog. Med. Chem.* **1998**, *35*, 199. Lambert, D.M. *Curr. Med. Chem.* **1999**, *6*, 635. Mechoulam, R. *et al., Eur. J. Pharmacol.* **1998**, *359*, 1. Williamson, E.M. and Evans, F.J. *Drugs* **2000**, *60*, 1303. Pertwee, R.G. *Addiction Biology* **2000**, *5*, 37. Robson, P. *Br. J. Psychiatry* **2001**, *178*, 107. Pertwee, R. G. *Prog. Neurobiol.* **2001**, *63*, 569. Goya, P and Jagerovic, N. *Exp. Opin. Ther. Patents* **2000**, *10*, 1529. Pertwee, R. G. *Gut* **2001**, *48*, 859).

It has now surprisingly been found that potent and selective antagonism of cannabinoid-CB_1 receptors is present in the novel 4,5-dihydro-1H-pyrazole derivatives of the formula (Ia) or (Ib), prodrugs thereof, tautomers thereof and salts thereof



(Ia) (Ib)

wherein

- R and R_1 independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group C_{1-3}-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C_{1-2})-amino, mono- or dialkyl (C_{1-2})-amido, (C_{1-3})-alkyl sulfonyl, dimethylsulfamido, C_{1-3}-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or R_1 represent naphtyl,
- R_2 represents hydrogen, hydroxy, C_{1-3}-alkoxy, acetyloxy or propionyloxy,
- R_3 represents a hydrogen atom or a branched or unbranched C_{1-8} alkyl group or a C_{3-7} cycloalkyl group which alkyl group or cycloalkyl group may be substituted with a hydroxy group,
- R_4 represents a hydrogen atom or a branched or unbranched C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{2-10} heteroalkyl, C_{3-8} nonaromatic heterocycloalkyl or C_{4-10} nonaromatic heterocycloalkyl-alkyl moiety which moieties may contain one or more heteroatoms from the group (O, N, S), which moieties may be substituted with a keto group, trifluoromethyl group, C_{1-3} alkyl group, hydroxy, amino, monoalkylamino, or dialkylamino group or a fluoro atom, or R_4 represents an amino, hydroxy, phenoxy or benzyloxy group or R_4 represents a branched or

unbranched C_{1-8} alkoxy, C_{3-8} alkenyl, C_{5-8} cycloalkenyl or C_{6-9} cycloalkenylalkyl group which groups may contain a sulphur, nitrogen or oxygen atom, a keto group or $-SO_2-$ group which C_{1-8} alkoxy, C_{3-8} alkenyl, C_{5-8} cycloalkenyl or C_{6-9} cycloalkenylalkyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom, or R_4 represents a phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group wherein the aromatic rings may be substituted with 1, 2 or 3 of the substituents Y, wherein Y has the meaning as indicated above, or

R_4 represents a group NR_8R_9 with the proviso that R_3 represents a hydrogen atom or a methyl group and wherein R_8 and R_9 are the same or different and represent C_{1-4} alkyl or C_{2-4} trifluoroalkyl or R_8 and R_9 - together with the nitrogen atom to which they are bonded - form a saturated or un-saturated heterocyclic moiety having 4 to 8 ring atoms which heterocyclic moiety may contain an oxygen or sulphur atom or a keto group or $-SO_2-$ group or an additional nitrogen atom, which saturated or unsaturated heterocyclic moiety may be substituted with a C_{1-4} alkyl group or

R_3 and R_4 - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic moiety may contain one or more atoms from the group (O, N, S) or a keto group or $-SO_2-$ group, which moiety may be substituted with a C_{1-4} alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidinyl, pyrrolidinyl, piperidinyl or hexahydro-1H-azepinyl group,

- R_5 and R_6 independently of each other represent a hydrogen atom or a branched or unbranched C_{1-8} alkyl or alkenyl group which groups may contain one or more heteroatoms from the group (O, N, S), a keto group or a $-SO_2-$ group and which groups may be substituted with a hydroxy or amino group, or R_5 and R_6 independently of each other represent a C_{3-8} cycloalkyl group or C_{3-8} cycloalkenyl group which may contain one or more ring heteroatoms from the group (O, N, S) or the $-SO_2-$ group and which groups may be substituted with a hydroxy group, alkyl (C_{1-3}), the $-SO_2-$ group, the keto group, amino group, monoalkylamino group (C_{1-3}) or dialkylamino group (C_{1-3}), or

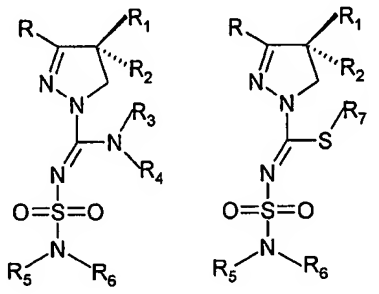
R_5 represents a naphtyl group or a phenyl group which phenyl group may be substituted with 1, 2 or 3 substituents Y wherein Y has the meaning as described hereinabove, with the proviso that R_6 represents a hydrogen atom, or a branched or unbranched alkyl group (C_{1-5}) which alkyl group may contain one or more heteroatoms from the group (O, N, S) or the $-SO_2-$ group and which alkyl group may be substituted with a hydroxy, keto or amino group, or

R_5 and R_6 - together with the nitrogen atom to which they are bonded - form a monocyclic, bicyclic or tricyclic alkyl or alkenyl group which may contain ring heteroatoms from the group (O, N, S), the keto or the SO_2 group and which

monocyclic, bicyclic or tricyclic alkyl or alkenyl group may be substituted with a hydroxy group, alkyl (C_{1-3}) group, SO_2 group, keto group, amino group, monoalkylamino group (C_{1-3}), dialkylamino group (C_{1-3}), pyrrolidinyl group or piperidinyl group, which monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain an annelated phenyl group which annelated phenyl group may be substituted with 1 or 2 substituents Y, wherein Y has the meaning as described herein above,

- R_7 represents branched or unbranched C_{1-3} alkyl.

At least one centre of chirality is present (at the C_4 position of the 4,5-dihydro-1H-pyrazole moiety) in the compounds of the formula (Ia) and (Ib). The invention relates both to racemates, mixtures of diastereomers and the individual stereoisomers of the compounds having formula (Ia) or (Ib). Particular compounds of interest of formula (Ia) or (Ib) have the absolute stereoconfiguration at the C_4 position of the 4,5-dihydro-1H-pyrazole moiety as represented by the formulas (1a*) and (1b*):



(1a*) (1b*)

The invention also relates both to the E isomer, Z isomer and E/Z mixtures of compounds having formula (Ia) or (Ib).

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

Due to the potent CB_1 antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetence, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelinisation related disorders, as well as for the treatment of pain disorders,

including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders.

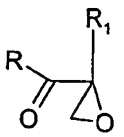
The affinity of the compounds of the invention for cannabinoid CB_1 receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid CB_1 receptor is stably transfected in conjunction with [^{3}H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [^{3}H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

The cannabinoid CB_1 antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB_1 receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB_1 receptors by CB_1 receptor agonists (*e.g.* CP-55,940 or (R)-WIN-55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This CB_1 receptor-mediated response can be antagonised by CB_1 receptor antagonists such as the compounds of the invention.

Intermediates having formula (II) (see below) can be obtained according to methods known, for example: a) Francotte, E.; Tong, Z. *Chem. Abstr.* **126**, 213598; b) Rempfler, H. and Kunz, W. *Chem. Abstr.* **113**, 40432; c) Rempfler, H. and Kunz, W. *Chem. Abstr.* **107**, 217473.

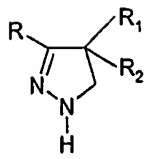
Intermediates having formula (III) wherein R_2 represents hydrogen (see below) can be obtained according to methods known, for example: a) EP 0021506; b) DE 2529689, c) Grosscurt, A.C. et al., *J. Agric. Food Chem.* **1979**, *27*, (2), 406.

Intermediates having formula (III) wherein R_2 represents a hydroxy group can be obtained by reacting a compound having formula (II) with hydrazine or hydrazine hydrate



(II)

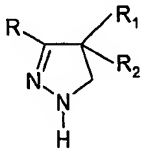
This reaction, preferably carried out in an organic solvent such as ethanol, yields a compound having formula (III) wherein R_2 represents a hydroxy group.


(III)

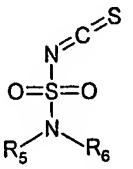
Suitable synthetic routes for the compounds of the invention are the following:

Synthetic route A

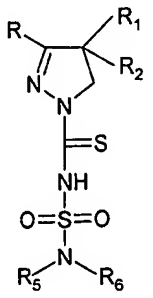
Step 1: reaction of a compound having formula (III)


(III)

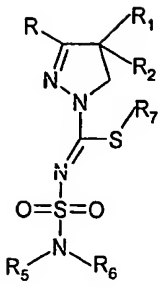
with a compound having formula (IV).


(IV)

This reaction is preferably carried out in an organic solvent, such as for example dichloromethane, and yields a compound having formula (V) wherein R, R_1, R_2, R_5 and R_6 have the meaning as described above for compound (Ia), and which are new.


(V)

Step 2: reaction of a compound having formula (V) with a compound R_7-X, wherein X represents a leaving group, for example an iodide group, and R_7 has the meaning as described above for (Ib) gives a compound having formula (Ib).



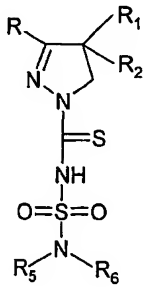
(Ib)

This reaction is preferably carried out in the presence of a base, for example triethylamine.

Step 3: reaction of a compound having formula (Ib) with an amine having formula HNR_3R_4 wherein R_3 and R_4 have the meanings as described above, analogous to the method described in *Synth. Commun.* **1996**, 26, (23), 4299.
This reaction gives a compound having formula (Ia).

Synthetic route A1

Step 1: Reaction of a compound having formula (V)



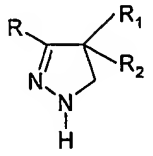
(V)

with an amine having formula HNR_3R_4 wherein R_3 and R_4 have the meanings as described above in the presence of a mercury(II) salt, for example $HgCl_2$, gives a compound having formula (Ia).

This reaction is preferably carried out in an organic solvent, such as for example acetonitrile, analogous to the method described in *Synth. Commun.* **1996**, *26*, (23), 4299.

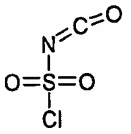
Synthetic route A2

Step 1: reaction of a compound having formula (III)



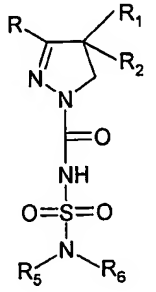
(III)

with a isocyanate derivative having formula (VI), followed by treatment with an amine HNR_5R_6



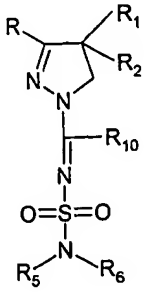
(VI)

This reaction is preferably carried out in an organic solvent like dichloromethane, and yields a compound having formula (VII). Compounds having formula (VII) wherein R, R_1, R_2, R_5 and R_6 have the meaning as described herein above for compound (Ia) are new.



(VII)

Step 2: reaction of a compound having formula (VII) with a halogenating agent, such as for example PCl_5, gives a compound having formula (VIII)



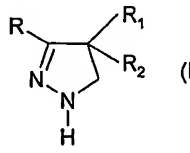
(VIII)

wherein R_{10} represents a halogen atom, for example a chloro atom. This reaction is preferably carried out in an organic solvent such as chlorobenzene.
Compounds having formula (VIII) wherein R, R_1, R_2, R_5 and R_6 have the meanings as described above for compound (Ia) and wherein R_{10} represents a halogen atom, are new.

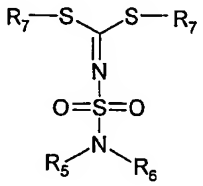
Step 3: reaction, preferably carried out in an inert organic solvent such as dichloromethane, of a compound having formula (VIII) with an amine having formula HNR_3R_4 wherein R_3 and R_4 have the meanings as described above gives a compound having formula (Ia).

Synthetic route A3

Step 1: reaction of a compound having formula (III)


(III)

with a compound having formula (IX)


(IX)

gives a compound having formula (Ib), (see e.g. *Chem. Ber.* **1966**, *99*, 2885 and *Chem. Ztg.* **1984**, *108*, (12), 404).

The preparation of the compounds is illustrated in the following examples.

Example 1

3-(4-Chlorophenyl)-N'-(((ethyl)propylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine

Part A: To a stirred solution of ((ethyl)propylamino)sulfonyl isothiocyanate (5.98 gram, 25.4 mmol) in dry dichloromethane in a nitrogen atmosphere is added of 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (6.52 gram, 25.4 mmol). After stirring for 90 minutes the resulting solution is concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2, silicagel, R_f ~0.45). The resulting solid is recrystallized from diethyl ether to give 3-(4-chlorophenyl)-N-

(((ethyl)propylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyra-zole-1-thiocarboxamide (6.57 gram, 56 % yield). Melting point: 144-146 °C.

Part B: To a stirred suspension of 3-(4-chlorophenyl)-N-(((ethyl)propyl-amino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (2.32 gram, 5 mmol) in acetonitrile (20 mL) is added cold methylamine (4 mL). To the resulting solution is added a solution of $HgCl_2$ (1.5 gram) in acetonitrile (10 mL). The resulting black suspension is stirred for four hours. The precipitate is removed by filtration. The filtrate is concentrated *in vacuo*, dissolved in dichloromethane and successively washed with aqueous 0.5 N NaOH solution and water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting oil is crystallized from diethyl ether to give 3-(4-chlorophenyl)-N'-(((ethyl)propylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (1.78 gram, 77 % yield). Melting point (MP):129-131 °C.

In an analogous manner the compounds having formula (Ia) listed below have been prepared:

2. 3-(4-Chlorophenyl)-N'-(((ethyl)methylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 112-115 °C.
3. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(2-hydroxyethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 104-106 °C.
4. 3-(4-Chlorophenyl)-N-(2-hydroxyethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 490 (MH^+).
5. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(2-(morpholin-4-yl)ethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 547 (MH^+))
6. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(2-(morpholin-4-yl)ethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
7. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(2-(dimethylamino)ethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine.MS (ESI+): 505 (MH^+)).
8. 3-(4-Chlorophenyl)-N-(3-(dimethylamino)propyl)-N'-((dimethylamino)sulfo-nyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
9. 3-(4-Chlorophenyl)-N-(2-(piperidin-1-yl)ethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 557 (MH^+)).
10. 3-(4-Chlorophenyl)-N-(2-(morfolin-4-yl)ethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 559 (MH^+)); MP: 174-176 °C.
11. 3-(4-Chlorophenyl)-N-(2-(dimethylamino)ethyl)-N'-((dimethylamino)sulfo-nyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
12. 3-(4-Chlorophenyl)-N-(2-(diethylamino)ethyl)-N'-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
13. 3-(4-Chlorophenyl)-N-(3-(dimethylamino)propyl)-N'-((diethylamino)sulfo-nyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine.MS(ESI+):519 (MH^+).

14. 3-(4-Chlorophenyl)-N-(2-(diethylamino)ethyl)-N'-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine hemifumarate. MP: 182-185 °C.
15. 3-(4-Chlorophenyl)-N-(2-(dimethylamino)ethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
16. 3-(4-Chlorophenyl)-N-(2-(diethylamino)ethyl)-N'-((pyrrolidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
17. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(1-methylpiperidin-4-yl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
18. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(2-hydroxyethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 123-126 °C.
19. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous. R_f ~ 0.4 (diethyl ether).
20. 3-(4-Chlorophenyl)-N'-(((ethyl)propylamino)sulfonyl)-N-Methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 129-131 °C.
21. 3-(4-Chlorophenyl)-N-methyl-N'-((pyrrolidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous. R_f ~ 0.3 (MTBE).
22. 3-(4-Chlorophenyl)-N-methyl-N'-(((methyl)propylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 132-134 °C.
23. 3-(4-Chlorophenyl)-N,N-dimethyl-N'-((pyrrolidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous. R_f ~ 0.25 (MTBE).
24. 3-(4-Chlorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 175-177 °C.
25. 3-(4-Chlorophenyl)-N'-((hexahydro-1H-azepin-1-yl)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
26. 3-(4-Chlorophenyl)-N'-((dipropylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 141-142 °C.
27. 3-(4-Chlorophenyl)-N'-(((isopropyl)methylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 134-136 °C.
28. 3-(4-Chlorophenyl)-N-methyl-N'-((octahydroazocin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 165-168 °C.
29. 3-(4-Chlorophenyl)-N-ethyl-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
30. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 166-168 °C.

Example 31

3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-propyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine

Part A: To a stirred solution of chlorosulfonyl isocyanate (1.73 mL, 20 mmol) in dry dichloromethane (20 mL) is very slowly added a solution of 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (5.13 gram, 20 mmol) in dry dichloromethane (125 mL) at – 5 °C. After stirring for 30 minutes the reaction mixture is allowed to attain

room temperature and stirred for another 2 hours. After cooling to 0 °C liquid dimethylamine (5 mL) is added and the resulting solution is stirred for another hour at 0 °C and for 2 hours at room temperature. The solution is washed with water, filtered over hyflo and concentrated *in vacuo*. Flash chromatography (MTBE, R_f ~ 0.3) gives 3-(4-chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (4.75 g, 58 %). MP: 210-212 °C.

Part B: A mixture of 3-(4-chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1.47 gram, 3.62 mmol) and phosphorus pentachloride (0.80 gram, 3.84 mmol) in chlorobenzene (20 mL) is heated at reflux temperature for 1 hour. After thorough concentration *in vacuo*, the formed 3-(4-chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidoyl chloride is suspended in dry dichloromethane and reacted with cold *n*-propylamine (1.0 mL) at 0 °C. After stirring for 1 hour, the mixture is dissolved in ethyl acetate and washed with water and concentrated *in vacuo*. The residue is purified by column chromatography (dichloromethane/acetone = 19/1 (v/v), R_f ~ 0.35) to give an oil (0.82 g). Crystallisation from diethyl ether, followed by recrystallisation from ethanol gives 3-(4-chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-propyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (0.38 gram, 23 % yield). MP: 127-129°C.

In an analogous manner the compounds having formula (Ia) listed below have been prepared:

32. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(2-fluoroethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 128-131 °C.
33. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-4-phenyl-N-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 158-159 °C.
34. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methoxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 170-172 °C.

Example 35

3-(4-Chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester

Part A: To a stirred solution of (piperidin-1-yl)sulfonyl isothiocyanate (54.77 g, 266 mmol) in dry dichloromethane (900 mL) in a nitrogen atmosphere is added 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (68.3 gram, 266 mmol). After stirring for 16 hours an additional amount of dichloromethane is added. The resulting solution is twice washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. After addition of MTBE, the residue crystallizes. The crystalline material is collected and washed with MTBE to give 3-(4-chlorophenyl)-4-phenyl-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (77.6 gram, 63 % yield).

Part B: To a stirred solution of 3-(4-chlorophenyl)-4-phenyl-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (30 gram, 64.9 mmol) in acetone (1 L) is added triethylamine (18.0 mL, 130 mmol). To the resulting yellow solution is added methyl iodide (9.12 g, 64 mmol) and the resulting solution is stirred

for 16 hours at room temperature. The formed precipitate is removed by filtration. The filtrate is washed with water, concentrated *in vacuo* to give a yellow solid. Recrystallisation from MTBE gives 3-(4-chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester (27.9 gram, 90% yield). MP: 192-194 °C.

In an analogous manner the compounds having formula (Ib) listed below have been prepared:

36. 3-(4-Chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 159-160 °C.
37. 3-(4-Chlorophenyl)-N-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 141-143 °C.
38. 3-(4-Chlorophenyl)-4-phenyl-N-((1,2,3,4-tetrahydroisoquinolin-2-yl)sulfonyl) -4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 143-145 °C.
39. 3-(4-Chlorophenyl)-N-(((ethyl)phenylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 143-146 °C.
40. 3-(4-Chlorophenyl)-N-((diethylamino)sulfonyl)-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
41. 3-(4-Chlorophenyl)-N-((diethylamino)sulfonyl)-4-(pyridin-4-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
42. 3-(4-Chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-(3-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
43. 3-(4-Chlorophenyl)-N-((dimethylamino)sulfonyl)-4-(3-(trifluoromethyl) phenyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
44. 3-(4-Chlorophenyl)-N-(((ethyl)methylamino)sulfonyl)-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester.MP:133-136 °C.
45. 3-(4-Chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 182-185 °C.
46. 3-(4-Chlorophenyl)-N-((morpholin-4-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 202-204 °C.
47. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP:205-207°C.
48. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP:196-198°C.
49. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-((dimethylamino)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP:181-183°C.
50. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP:231-233°C.
51. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP:221-225°C.

52. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-((dimethylamino)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP:181-185°C.
53. 3-(4-Chlorophenyl)-N-((1,1-dioxidothiomorpholin-4-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 216-217 °C.
54. 3-(5-Chlorothien-2-yl)-N-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.

Example 55

3-(4-Chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine

To a cooled mixture (< 0 °C) of 3-(4-chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester (10.0 gram, 21 mmol) in methanol (75 mL) is added cold methylamine (15 mL). The resulting mixture is allowed to attain room temperature and stirred for 3 hours at 50 °C. After cooling to room temperature the mixture is concentrated *in vacuo*, dissolved in dichloromethane, washed twice with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Subsequent flash chromatography (EtOAc/MeOH/NH_4OH (25 % aq.) = 95/5/0.5 (v/v)), followed by recrystallisation from diisopropyl ether gives 3-(4-chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine (7.87 gram, 81 % yield) as a white solid. MP: 175-177 °C.

In an analogous manner the compounds having formula (Ia) listed below - including those in table 1 - have been prepared:

56. 3-(4-Chlorophenyl)-N-cyclopropyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 142-144 °C.
57. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 180-182 °C.
58. 3-(5-Chlorothien-2-yl)-N'-((diethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 122-123 °C.
59. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 169-170 °C.
60. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(1-methylpiperidin-4-yl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 144-146 °C.
61. 3-(4-Chlorophenyl)-N-cyclopropyl-N'-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 150-151 °C.
62. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-ethyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 116-119 °C.
63. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N,N-dimethyl-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 135-137 °C.
64. N'-((Diethylamino)sulfonyl)-N,N-dimethyl-3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 159-160 °C.
65. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 81-85 °C.
66. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-ethyl,N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
67. 3-(4-Chlorophenyl)-N-ethyl,N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 178 °C.
68. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-ethyl-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 162-165 °C.
69. 3-(4-Chlorophenyl)-N-methyl-N'-((1,2,3,4-tetrahydroisoquinolin-2-yl)sulfo-nyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
70. 3-(4-Chlorophenyl)-N'-(((ethyl)phenylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 145-147 °C.

71. N'-((Diethylamino)sulfonyl)-3-(4-chlorophenyl)-N-methyl-4-(pyridin-4-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 109-111 °C.
72. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 157-159 °C.
73. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 85-89 °C.
74. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-(pyridin-4-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 178-182 °C.
75. 3-(4-Chlorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-(3-(trifluoro-methyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 168-170 °C.
76. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-(3-(trifluoro-methyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 65-68 °C.
77. 3-(4-Chlorophenyl)-N'-(((ethyl)methylamino)sulfonyl)-N-methyl-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 125-128 °C.
78. 3-(4-Chlorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 174-177 °C.
79. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-methyl-N'-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 223-235 °C.
80. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 214-216 °C.
81. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 260-263 °C.
82. 3-(4-Chlorophenyl)-4-(3-fluorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 170 °C.
83. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 223-225 °C.
84. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-4-(2-fluorophenyl)-N-methyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 173-175 °C.
85. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-4-(3-fluorophenyl)-N-methyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 110 °C.
86. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-methyl-N'-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 165-168 °C.
87. 3-(4-Chlorophenyl)-N'-((1,1-dioxidothiomorpholin-4-yl)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 268-271 °C.
88. 3-(4-Chlorophenyl)-N'-((4-hydroxypiperidin-1-yl)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 80 °C.

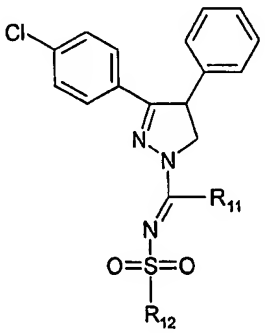


Table 1

Example:	R_{11}	R_{12}	MP (°C)	Salt form
89:	4-Methyl-1,4-diazepan-1-yl	Dimethylamino	197-200	0.5 Fumarate
90:	1,4-Diazepan-1-yl	Piperidin-1-yl	Amorphous	
91:	1,4-Diazepan-1-yl	Dimethylamino	Amorphous	
92:	4-Methyl-1,4-diazepan-1-yl	Piperidin-1-yl	159-164	

93:	4-Methylpiperazin-1-yl	Dimethylamino	191-193	

Example 94

3-(4-Chlorophenyl)-N-((4-methylpiperazin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester

Part A: A stirred mixture of 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (3.21 gram, 11.3 mmol), [(4-methylpiperazin-1-yl)sulfonyl]dithioimido- carbonic acid dimethyl ester (3.08 gram, 12.0 mmol) and pyridine (25 mL) is heated at 100 °C for 24 hours in a nitrogen atmosphere. After cooling to room temperature the mixture is concentrated *in vacuo*, water is added and the resulting mixture is extracted with dichloromethane. The dichloromethane extract is washed twice with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Subsequent flash chromatographic purification gives 3-(4-chlorophenyl)-N-((4-methylpiperazin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester (4.24 gram, 76 % yield) as an amorphous solid. (R_f ~ 0.1, EtOAc/methanol = 95/5 (v/v)).

In an analogous manner the compounds having formula (Ib) listed below have been prepared:

95. 3-(4-Chlorophenyl)-N-(((2-(dimethylamino)ethyl)ethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester.
MP: 158 °C.
96. N-((Diethylamino)sulfonyl)-3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
R_f ~ 0.4 (MTBE).
97. 3-(4-Chlorophenyl)-N-(([1,4']bipiperidin-1'-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 245 °C.
98. 3-(4-Chlorophenyl)-N-(((1-methylpiperidin-4-yl)methylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Oil. R_f ~ 0.15 (methanol/dichloromethane = 5/95 (v/v)).
99. 3-(4-Chlorophenyl)-N-((4-methyl-1,4-diazepan-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
R_f ~ 0.10 (methanol/dichloromethane = 5/95 (v/v)).

Example 100

(-)-(4S)-3-(4-Chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine

(-)-(4S)-3-(4-Chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine (3.8 gram, 8.3 mol)) ($[\alpha^{25}_D]$ = -139 °, c = 0.006, MeOH) was obtained as an amorphous solid via chiral chromatographic separation of racemic 3-(4-chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-

dihydro-1H-pyrazole-1-carboxamidine (7.87 gram, 17.1 mmol) using a chiral stationary phase Chiralpak AD. The mobile phase consisted of methanol/diethylamine = 999/1 (v/v).

In an analogous manner the optically pure compounds listed below have been prepared from the corresponding racemates:

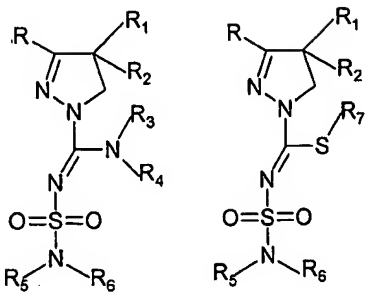
101. (-)-(4S)-3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (Chiral stationary phase: Chiralcel OD). Mobile phase consisted of hexane/2-propanol = 80/20 (v/v). ($[\alpha^{25}_D]$ = -147 °, c = 0.01, MeOH). Amorphous.

102. (-)-(4S)-3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (Chiral stationary phase: Chiralpak AD). The mobile phase consisted of methanol/diethylamine = 999/1 (v/v). ($[\alpha^{25}_D]$ = -171 °, c = 0.005, MeOH). Amorphous.

103. (-)-(4S)-3-(4-Chlorophenyl)-N-methyl-N'-((morpholin-4-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. ($[\alpha^{25}_D]$ = -144 °, c = 0.01, MeOH). (Chiral stationary phase: Chiralpak AD). The mobile phase consisted of ethanol. Amorphous.

Claims

1. Compounds of the general formulas (Ia) or (Ib)



(Ia) (Ib)

wherein

- R and R_1 independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group C_{1-3}-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C_{1-2})-amino, mono- or dialkyl (C_{1-2})-amido, (C_{1-3})-alkyl sulfonyl, dimethylsulfamido, C_{1-3}-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or R_1 represent naphtyl,
- R_2 represents hydrogen, hydroxy, C_{1-3}-alkoxy, acetyloxy or propionyloxy,
- R_3 represents a hydrogen atom or a branched or unbranched C_{1-8} alkyl group or a C_{3-7} cycloalkyl group which alkyl group or cycloalkyl group may be substituted with a hydroxy group,
- R_4 represents a hydrogen atom or a branched or unbranched C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{2-10} heteroalkyl, C_{3-8} nonaromatic heterocycloalkyl or C_{4-10} nonaromatic heterocycloalkyl-alkyl moiety which moieties may contain one or more heteroatoms from the group (O, N, S), which moieties may be substituted with a keto group, trifluoromethyl group, C_{1-3} alkyl group, hydroxy, amino, monoalkylamino, or dialkylamino group or a fluoro atom, or R_4 represents an amino, hydroxy, phenoxy or benzyloxy group or R_4 represents a branched or unbranched C_{1-8} alkoxy, C_{3-8} alkenyl, C_{5-8} cycloalkenyl or C_{6-9} cycloalkenylalkyl group which groups may contain a sulphur, nitrogen or oxygen atom, a keto group or -SO_2- group which C_{1-8} alkoxy, C_{3-8} alkenyl, C_{5-8} cycloalkenyl or C_{6-9} cycloalkenylalkyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom, or R_4 represents a phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group wherein the aromatic rings may be substituted with 1, 2 or 3 of the substituents Y, wherein Y has the meaning as indicated above, or

R_4 represents a group NR_8R_9 with the proviso that R_3 represents a hydrogen atom or a methyl group and wherein R_8 and R_9 are the same or different and represent C_{1-4} alkyl or C_{2-4} trifluoroalkyl or R_8 and R_9 - together with the nitrogen atom to which they are bonded - form a saturated or un-saturated heterocyclic moiety having 4 to 8 ring atoms which heterocyclic moiety may contain an oxygen or sulphur atom or a keto group or $-SO_2-$ group or an additional nitrogen atom, which saturated or unsaturated heterocyclic moiety may be substituted with a C_{1-4} alkyl group or

R_3 and R_4 - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic moiety may contain one or more atoms from the group (O, N, S) or a keto group or $-SO_2-$ group, which moiety may be substituted with a C_{1-4} alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidinyl, pyrrolidinyl, piperidinyl or hexahydro-1H-azepinyl group,

- R_5 and R_6 independently of each other represent a hydrogen atom or a branched or unbranched C_{1-8} alkyl or alkenyl group which groups may contain one or more heteroatoms from the group (O, N, S), a keto group or a $-SO_2-$ group and which groups may be substituted with a hydroxy or amino group, or R_5 and R_6 independently of each other represent a C_{3-8} cycloalkyl group or C_{3-8} cycloalkenyl group which may contain one or more ring heteroatoms from the group (O, N, S) or the $-SO_2-$ group and which groups may be substituted with a hydroxy group, alkyl (C_{1-3}), the $-SO_2-$ group, the keto group, amino group, monoalkylamino group (C_{1-3}) or dialkylamino group (C_{1-3}), or

  R_5 represents a naphtyl group or a phenyl group which phenyl group may be substituted with 1, 2 or 3 substituents Y wherein Y has the meaning as described hereinabove, with the proviso that R_6 represents a hydrogen atom, or a branched or unbranched alkyl group (C_{1-5}) which alkyl group may contain one or more heteroatoms from the group (O, N, S) or the $-SO_2-$ group and which alkyl group may be substituted with a hydroxy, keto or amino group, or

  R_5 and R_6 - together with the nitrogen atom to which they are bonded - form a monocyclic, bicyclic or tricyclic alkyl or alkenyl group which may contain ring heteroatoms from the group (O, N, S), the keto or the SO_2 group and which monocyclic, bicyclic or tricyclic alkyl or alkenyl group may be substituted with a hydroxy group, alkyl (C_{1-3}) group, SO_2 group, keto group, amino group, monoalkylamino group (C_{1-3}), dialkylamino group (C_{1-3}), pyrrolidinyl group or piperidinyl group, which monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain an annelated phenyl group which annelated phenyl group may be substituted with 1 or 2 substituents Y, wherein Y has the meaning as described herein above,

- R_7 represents branched or unbranched C_{1-3} alkyl.

and tautomers, stereoisomers, prodrugs and salts thereof.

2. Pharmaceutical compositions containing a pharmacologically active amount of at least one compound as claimed in claim 1 as an active component.

3. Method of preparing pharmaceutical compositions as claimed in claim 2 characterized in that a compound as claimed in claim 1 is brought in a form suitable for administration.

4. Process for the preparation of compounds having formula (Ib), characterized in that a compound is prepared wherein R, R_{1-2}, R_5-R_6 and R_7 have the meanings given in claim 1 by

   1) reacting a compound having formula (III) with a compound having formula (IV) to give a compound of the formula (V) which is reacted with a compound of the formula R_7-X, or

   2) reacting a compound having formula (III) with a compound having formula (IX).

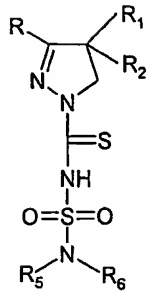
5. Process for the preparation of compounds having formula (Ia), characterized in that a compound is prepared wherein R and R_1-R_6 have the meanings given in claim 1 by

   1) reacting a compound having formula (Ib), with an amine of the formula HNR_3R_4, or

   2) reacting a compound having formula (V) with an amine of the formula HNR_3R_4 in the presence of a mercury (II) salt, or

   3) reacting a compound having formula (III) with a compound of the formula (VI) to give a compound of the formula (VII) which is reacted with a halogenating agent to give a compound of the formula (VIII) which is reacted with an amine of the formula HNR_3R_4.

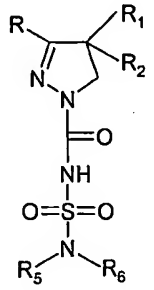
6. Compounds of the general formula (V)



(V)

wherein R, R_1, R_2, R_5 and R_6 have the meanings given in claim 1.

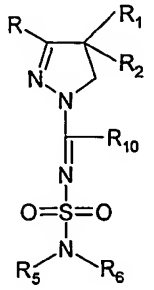
7. Compounds of the general formula (VII)



(VII)

wherein R, R_1, R_2, R_5 and R_6 have the meanings given in claim 1.

8. Compounds of the general formula (VIII)



(VIII)

wherein R, R_1, R_2, R_5 and R_6 have the meanings given in claim 1 and wherein R_{10} represents a halogen atom.

9. Use of a compound as claimed in claim 1 for the preparation of a pharmaceutical composition for the treatment of disorders involving cannabinoid neurotransmission.

10. Use as claimed in claim 9 characterised in that said disorders are psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetence, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelinisation related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/10435

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 .. A61K31/415 C07D231/06 C07D401/12 A61K31/4155 A61K31/4725 C07D401/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 70700 A (SOLVAY PHARMACEUTICALS B V) 27 September 2001 (2001-09-27) see the formula (i) definition for Aa, and formulae IX,VII and X (claims 8-10) ---	1-10
A	US 5 624 941 A (BARTH FRANCIS ET AL) 29 April 1997 (1997-04-29) the whole document ---	1-10
A	US 4 070 365 A (VAN DAALEN JAN JOHANNES ET AL) 24 January 1978 (1978-01-24) the whole document ---	1-10
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2002	29/11/2002

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	PERTWEE R G: "PHARMACOLOGY OF CANNABINOID RECEPTOR LIGANDS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 6, no. 8, August 1999 (1999-08), pages 635-664, XP000923352 ISSN: 0929-8673 cited in the application see page 641 ---	1-10
A	WO 00 46209 A (SANOFI SYNTHELABO ;BARTH FRANCIS (FR); CAMUS PHILIPPE (FR); MARTIN) 10 August 2000 (2000-08-10) the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/10435

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0170700 A	27-09-2001	AU	4250101 A	03-10-2001
		WO	0170700 A1	27-09-2001
		US	2001053788 A1	20-12-2001
US 5624941 A	29-04-1997	FR	2692575 A1	24-12-1993
		FR	2713224 A1	09-06-1995
		FR	2713225 A1	09-06-1995
		AT	149489 T	15-03-1997
		AU	4143893 A	06-01-1994
		BR	1100409 A3	13-10-1999
		BR	9302435 A	11-01-1994
		CA	2098944 A1	24-12-1993
		CZ	9301172 A3	16-03-1994
		DE	69308395 D1	10-04-1997
		DK	576357 T3	15-09-1997
		EP	0576357 A1	29-12-1993
		ES	2101258 T3	01-07-1997
		FI	932891 A	24-12-1993
		GR	3023535 T3	29-08-1997
		HU	64526 A2	28-01-1994
		IL	106099 A	15-07-1998
		JP	3238801 B2	17-12-2001
		JP	6073014 A	15-03-1994
		MX	9303664 A1	31-01-1994
		NO	932296 A	27-12-1993
		NZ	247961 A	28-08-1995
		RU	2119917 C1	10-10-1998
		SK	65493 A3	02-02-1994
		ZA	9304511 A	22-02-1994
		AT	154012 T	15-06-1997
		AU	685518 B2	22-01-1998
		AU	7899994 A	15-06-1995
		BR	1100984 A3	14-03-2000
		CA	2136893 A1	21-06-1995
		CN	1110968 A ,B	01-11-1995
		CZ	9403016 A3	14-06-1995
		DE	69403614 D1	10-07-1997
		DE	69403614 T2	22-01-1998
		DK	656354 T3	29-12-1997
		EP	0656354 A1	07-06-1995
		ES	2105575 T3	16-10-1997
		FI	945690 A	03-06-1995
		GR	3024470 T3	28-11-1997
		HK	1000599 A1	09-04-1998
		HU	71498 A2	28-11-1995
		IL	111719 A	28-10-1999
		JP	3137222 B2	19-02-2001
		JP	7309841 A	28-11-1995
		JP	2001026541 A	30-01-2001
		NO	944625 A	06-06-1995
		NZ	270025 A	26-09-1995
		PL	306067 A1	12-06-1995
		RU	2141479 C1	20-11-1999
		SG	68570 A1	20-06-2000
US 4070365 A	24-01-1978	NL	7409433 A	14-01-1976
		AR	223449 A1	31-08-1981
		AT	359775 B	25-11-1980

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/EP 02/10435

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4070365 A		AT 508277 A	15-04-1980
		AT 342585 B	10-04-1978
		AT 529175 A	15-08-1977
		AU 501280 B2	14-06-1979
		AU 8285075 A	13-01-1977
		BE 831232 A1	12-01-1976
		BR 7504413 A	06-07-1976
		CA 1075242 A1	08-04-1980
		CH 624675 A5	14-08-1981
		CS 188962 B2	30-03-1979
		DD 122775 A5	05-11-1976
		DE 2529689 A1	29-01-1976
		DK 310975 A ,B,	13-01-1976
		EG 11880 A	30-09-1978
		ES 439292 A1	16-02-1977
		FR 2277827 A1	06-02-1976
		GB 1514285 A	14-06-1978
		HU 178320 B	28-04-1982
		IE 41836 B1	09-04-1980
		IL 47676 A	31-01-1979
		IT 1044358 B	20-03-1980
		JP 1368569 C	11-03-1987
		JP 51041358 A	07-04-1976
		JP 61023162 B	04-06-1986
		OA 5057 A	31-12-1980
		PL 105891 B1	30-11-1979
		PL 193676 A1	17-07-1978
		SE 419644 B	17-08-1981
		SE 7507868 A	13-01-1976
		US 4156007 A	22-05-1979
		YU 176475 A1	30-06-1982
		ZA 7504203 A	23-02-1977
WO 0046209 A	10-08-2000	FR 2789078 A1	04-08-2000
		FR 2789079 A1	04-08-2000
		AU 2298900 A	25-08-2000
		BG 105749 A	28-02-2002
		BR 0007895 A	30-10-2001
		CN 1346349 T	24-04-2002
		CZ 20012697 A3	17-10-2001
		EE 200100399 A	15-10-2002
		EP 1150961 A1	07-11-2001
		WO 0046209 A1	10-08-2000
		HR 20010564 A1	31-08-2002
		NO 20013736 A	28-09-2001
		NZ 512886 A	25-10-2002
		SK 10872001 A3	03-12-2001
		TR 200102054 T2	21-05-2002
		US 6432984 B1	13-08-2002